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New Narcotic Drugs and Their International Control

Since the international conventions on narcotics were drawn up, chemistry has created new narcotics. The following article describes the mechanism by which the production of, and the trade in those new drugs can be brought under international control.

I. Introduction

A noteworthy feature in the international instruments on narcotic drugs is the machinery for bringing new narcotic drugs under international control without the formalities of new treaties.

The instruments which provide for such machinery are the International Opium Convention signed at The Hague on 23 January 1912, the Convention signed at Geneva on 19 February 1925, the Convention for Limiting the Manufacture and Regulating the Distribution of Narcotic Drugs signed at Geneva on 13 July 1931 and the Protocol signed in Paris on 19 November 1948, Bringing under International Control Drugs Outside the Scope of the Convention of 13 July 1931 for Limiting the Manufacture and Regulating the Distribution of Narcotic Drugs.

The authors of these international treaties realized that due to the march of progress in chemistry and pharmacology new narcotic drugs which were outside the scope of the existing conventions were being rapidly discovered and that the provision in these treaties of some device for bringing these new narcotic drugs under control was not only desirable but also necessary.

In order to fulfil its purpose, such machinery must operate with speed and effectiveness. The cumbersome procedure of amending the existing treaties or of concluding a new treaty in order to subject a newly-discovered narcotic drug to international control must therefore be avoided.

The making and improvement of this machinery from its first simple model to its present effectiveness was a slow process. It took almost forty years.

During this period, altogether four attempts were made to solve the problem of new drugs. These four attempts may be briefly described as follows:

II. First attempt: Article 14 (d) of the International Opium Convention signed at The Hague on 23 January 1912

This article provides that the "Contracting Powers shall apply the laws and regulations respecting the manufacture, import, sale, export of morphine, cocaine, and their respective salts: . . . (*d*) To all new derivatives of morphine, of cocaine, or of their respective salts, and to every other alkaloid of opium, which may be shown by scientific research, generally recognized, to be liable to similar abuse and productive of like ill effects".

This first instrument did not have the direct effect of bringing new drugs under the Hague Convention. It merely imposed on the States Parties the obligation of applying their existing national narcotic laws, if any, on such new drugs, which were applied to drugs mentioned in the Convention.

The machinery for determining the addiction-producing quality of new drugs, as provided for in this article, was national and not international. Drugs suspected of producing addiction were not subject to international scientific study or analysis. No declaration or pronouncement on the addiction-producing quality of drugs by an international body of experts was required. The effect was that a State would be bound to apply its existing narcotic laws to a new drug if it had within its territory modern facilities for scientific research defining the addiction-producing quality of such drugs, while another State would not be bound to do so, if it did not possess these facilities.

Moreover, the machinery as provided in article 14 (*d*) of The Hague Convention was restricted in its application. It could only deal with new derivatives

of morphine, of cocaine, or of their respective salts, and every other alkaloid of opium. It could not, for instance, deal with the preparations of Indian hemp or synthetic drugs.

III. Second attempt: Article 10 of the Convention signed at Geneva on 19 February 1925

The machinery for bringing new narcotic drugs under international control as provided for in the Geneva Opium Convention of 1925, which was initiated under the auspices of the League of Nations, was certainly an improvement over the first attempts in The Hague Convention of 1912.

In the first place, the new machinery is broader in its application than that of the Hague Convention. While article 14 (*d*) of The Hague Convention was only applicable to "new derivatives of morphine, of cocaine and their respective salts and to every other alkaloid of opium", article 10 of the 1925 Convention is applicable to "any narcotic drug to which the present Convention does not apply".

Secondly, under article 10 of the Geneva Opium Convention the determination or finding of the addiction-producing quality of a drug as a condition precedent to international control is entrusted to international bodies of experts instead of domestic or national institutions.

During the life of the League of Nations these international bodies of experts were the Office international d'hygiène publique and the Health Committee of the League of Nations.

When the United Nations succeeded the League of Nations, these bodies were replaced by the World Health Organization and its Expert Committee on Drugs Liable to Produce Addiction.

Under article 10, the services of the World Health Organization are placed for this purpose at the disposal of all States Parties to that Convention. Any State Party may, therefore, set the machinery in motion by drawing the attention of the World Health Organization to drugs suspected of possessing addiction-producing qualities.

The notification of the finding by the World Health Organization and the communication of its recommendation to governments is handled through the instrumentality of the organs of the United Nations. For instance, when the World Health Organization, on the advice of its Expert Committee, finds that a drug is addiction-producing it informs, through the Secretary-General of the United Nations, the Economic and Social Council of its finding and recommends that the drug be subject to international control in accordance with that Convention. The Council, in turn, communicates through the Secretary-General the recommendation to the States Parties. States Parties may notify the Secretary-General of their acceptances. When the Secretary-General notifies the Parties of these acceptances, the drug is under international control in so far as the States having accepted the recommendation are concerned.

Under article 10, the recommendation of the World Health Organization in respect of a new narcotic drug has to be accepted by States before it becomes binding on them, and it is a well-known fact that such recommendations are generally accepted. For instance, the recommendation in respect of pethidine was accepted by all the States Parties to the Geneva Opium Convention. In addition, several States non-Parties also accepted the recommendation.

The following drugs were brought under control in accordance with the Geneva Opium Convention of 1925 under article 10 of that Convention:[1]

Eucodal and its preparations;

Dicodide and its preparations;

Dilaudide;

Preparations based on Indian hemp extract or tincture;

Benzoyl-morphine and other esters of morphine;

Acedicone, its salts and preparations;

Drugs in article I, paragraph 2, group I of the Limitation Convention;

Desomorphine;

Pethidine (dolantine, demerol).

By legal interpretation,[2] article 10 of the Geneva Opium Convention is not applicable to a drug not itself addiction-producing but convertible into a drug capable of producing addiction.

IV. Third attempt: Article 11 of the Convention of 13 July 1931 for Limiting the Manufacture and Regulating the Distribution of Narcotic Drugs

The machinery provided in this article operates in two stages, namely, the national and the international.

In the first stage, the State Party concerned has to employ the facilities of scientific or medical research available within its territory to determine "to its satisfaction" whether or not the product in question[3] is of medical or scientific value, and whether or not it is capable of producing addiction or of conversion into a product capable of producing addiction.

If the result of the investigation reveals that the product is of medical or scientific value but capable

[1] See O.C. 1411, League of Nations document.

[2] Report of the Advisory Committee on traffic in opium and other dangerous drugs of the League of Nations (twenty-first session), page 15.

[3] The drug must be a product derived either from the group known as the phenanthrene alkaloids of opium or from the other group known as the ecgonine alkaloids of the coca leaf.

of producing addiction or of conversion into a product capable of producing addiction, the State concerned may for the time being authorize (by licence for instance) its manufacture limited to domestic medical and scientific needs and to quantities required for export orders in accordance with the provisions of the Convention. In other words, even at this first stage the provisions of the Convention already apply to this drug.

If the result of the investigation is negative, the provisions of the Convention do not apply.

In the second stage, the services of the international bodies of experts and of the organs of the United Nations are brought into play.

When the government concerned issues a licence permitting the manufacture of the product in question in the circumstances described above, it shall immediately notify the Secretary-General of the United Nations to that effect, and the Secretary-General shall in turn advise the other Contracting Parties and the World Health Organization. Thereupon, the World Health Organization refers the notification to its Expert Committee on Drugs Liable to Produce Addiction for study and advice.

If the World Health Organization, acting on the advice of its Expert Committee, decides that the product in question is capable of producing addiction, it shall so notify the Secretary-General, who will in turn communicate the notification to the States Parties to the Convention, both Members and non-members of the United Nations. Upon receipt of this communication, the product in question falls under article I, paragraph 2, group I, of the Convention and the States Parties are under obligation to apply to the product the laws which are applied to the drugs in group I.

If, however, the World Health Organization, acting on the advice of its Expert Committee, decides that the product in question is not itself capable of producing addiction but is convertible into such a drug, it must refer to a body[4] of three experts the question whether this product falls under sub-group (*b*) of group I or under group II.

When the three experts decide that the product falls under sub-group (*b*) of group I or group II, such decision shall be notified to the Secretary-General, who, in turn, will notify the States Parties. Upon receipt of such notification, the States Parties shall apply the appropriate provisions of the Convention according to whether the product falls under group I (*b*) or group II.

The following drugs have been brought under the Limitation Convention of 1931 through the application of article 11 as group I (*a*) drugs: Desomorphine and methyldihydromorphinone hydrochloride (metopon hydrochloride).

A few general observations may be made concerning the machinery provided for in article 11 of the Limitation Convention of 1931.

In the first place, the decisions of the expert bodies virtually placing new narcotic drugs under the Limitation Convention of 1931 are binding on the States Parties to that Convention after they have been published by the Secretary-General. They are not mere recommendations which should be accepted by the Contracting Parties, as in article 10 of the 1925 Convention.

Secondly, the product in question is examined and studied by both national and international expert institutions, which are available to all States Parties.

Thirdly, the provisions of the Convention apply immediately and provisionally during the interim period when the product is under study by the World Health Organization and its Expert Committee on Drugs Liable to Produce Addiction. During this interim period, only limited manufacture or trade is permitted.

It is, however, limited in application. The wording of article 11 is such that the machinery provided therein could only deal with new derivatives of morphine or of their respective salts, and every other alkaloid of opium, as well as with new derivatives of cocaine. It cannot deal with new drugs made by synthetic processes, for instance.

V. Fourth attempt: Protocol signed in Paris on 19 November 1948 Bringing under International Control Drugs Outside the Scope of the Convention of 13 July 1931 for Limiting the Manufacture and Regulating the Distribution of Narcotic Drugs

This Protocol incorporates by reference both the machinery for bringing new drugs under international control and the control measures provided for in the Limitation Convention of 1931 with a few important modifications. The following general observations may be made of this new machinery in the Protocol.

In the first place, the machinery provided in this Protocol is applicable to all drugs outside the scope of the 1931 Convention; its application is not limited to those of the phenanthrene alkaloids of opium or ecgonine alkaloids of coca leaf as in article 11 of the 1931 Convention.

Secondly, pending the publication of the finding of the World Health Organization, the Commission on Narcotic Drugs is authorized to invoke in respect of the product in question interim control measures in accordance with the provisions of the Limitation Convention of 1931, if by a simple majority vote it decides to do so. Such decision by the Commission on

[4] The three experts are selected in the following manner: one member by the government concerned; one by the Commission on Narcotic Drugs, and the third by the two members.

Narcotic Drugs is binding on the States Parties to the Protocol.

Thirdly, the World Health Organization, on the advice of its Expert Committee on Drugs Liable to Produce Addiction, not only passes on drugs falling under article I, paragraph 2, group I of the 1931 Convention, for which the control measures are much more stringent, but also decides whether the product in question falls under article I, paragraph 2, group II. The body of three experts provided for in article 11 of the 1931 Convention in such a case is dispensed with in the application of the Protocol.

Fourthly, the improved machinery proves to be workable and to work with speed. Since the Protocol came into force on 1 December 1949, the machinery has been set in motion and has brought some fourteen narcotic drugs under international control.

To illustrate, it may be mentioned here that the Government of the United States, pursuant to article I, paragraph 1 of the Protocol, addressed on 17 October 1950 a notification to the Secretary-General stating that fourteen named[5] drugs, all of which are or may be used for medical or scientific purposes and to which the Convention of 13 July 1931 does not apply, are considered liable to the same kind of abuse and productive of the same kind of harmful effects as the drugs specified in article I, paragraph 2, of the said Convention. Certain reports on results of research from the United States Public Health Hospital at Lexington were submitted with the notification.

Upon receipt of this notification and the enclosures, the Secretary-General transmitted on 15 November 1950, the United States notification together with the aforementioned research reports to the other States Parties to the Protocol, to the Commission on Narcotic Drugs and to the World Health Organization.

In accordance with article I, paragraph 2, the World Health Organization found that ten of the fourteen named drugs were capable of producing addiction and, therefore, decided that these ten drugs should fall under the régime laid down in the 1931 Convention for the drugs specified in article I, paragraph 2, group I of that Convention; and further that two of the fourteen named drugs, dihydrocodeine and acetyldihydrocodeine, were convertible into drugs capable of producing addiction and, therefore, decided that these two drugs should fall under the régime laid down for the drugs in group II of said article.

As regards the remaining two drugs, NU-1932 and NU-2206, it was stated in the notification that the Expert Committee on Drugs Liable to Produce Addiction, of the World Health Organization, would consider them at its next session.

These findings by the World Health Organization were notified on 29 January 1951 to the Secretary-General who transmitted the notification on 5 March 1951 to the States Members of the United Nations and non-member States Parties to the Protocol. These drugs were subject to the international control according to the appropriate régime laid down in article I, paragraph 2 of the 1931 Convention, as soon as the communication of the Secretary-General reached the States Parties to the Protocol.

The two remaining drugs[6] on which the findings and decisions of the World Health Organization are yet to be notified have since been provisionally put under the régime laid down in the 1931 Convention for the drugs in group I, by the resolution of the Commission on Narcotic Drugs[7] taken in pursuance of article 2 of the Protocol during its sixth session held in New York from 10 April to 24 May 1951. In brief, within the short period of a few months all the fourteen drugs specified in the notification of 17 October 1950 of the Government of the United States have been put under international control.

VI. Conclusions

Experience over a period of forty years has thus shown that the machinery for bringing new narcotic drugs within the scope of international treaties is not only desirable but also necessary, so long as modern pharmacology and chemistry keep on discovering and developing new drugs which are not covered by the treaties already in force.

Such machinery obviates the necessity of amending the existing treaties or drawing up new treaties for the control of new drugs, as the procedure both for amending treaties and concluding new treaties is cumbersome and subject to delays, while the submission of a new narcotic drug to international control before it is admitted into the channels of trade is urgent.

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[5] The named drugs are: 1-methyl-4-phenyl-piperidine-4-carboxylic acid ethyl ester (in the form of the hydrochloride, known under the names of dolantin, demerol, pethidine, isonipecaine, etc.); 4-(3-hydroxyphenyl)-1-methyl-4-piperidyl ethyl ketone hydrochloride (known as ketobemidone); 1-methyl-4-metahydroxyphenyl-piperidine-4-carboxylic acid ethyl ester (known as bemidone); α-1, 3-dimethyl-4-phenyl-4-propionoxy piperidine (known as NU-1196, or nisentil); β-1, 3-dimethyl-4-phenyl-4-propionoxy piperidine (otherwise identified by symbol NU-1779); β-1-methyl-3-ethyl-4-phenyl-4-propionoxy piperidine (otherwise identified by symbol NU-1932); 4, 4-diphenyl-6-dimethylamino-heptanone-3 (also known as methadone, amidone, dolophine, adanon, etc.); 4, 4-diphenyl-5-methyl-6-dimethylamino-hexanone-3 (known as isoamidone); 6-dimethylamino-4, 4-diphenyl-3-heptanol (otherwise identified by symbol N.I.H.-2933); 6-dimethylamino-4, 4-diphenyl-3-acetoxyheptane (otherwise identified by symbol N.I.H.-2953); 6-morpholino-4, 4-diphenyl-3-heptanone (also known as CB-11, heptazone or heptalgin); 3-hydroxy-N-methyl morphinan (otherwise known under the symbol identification NU-2206); dihydrocodeine; and acetyldihydrocodeine.

[6] NU-1932 and NU-2206.

[7] Report to the Economic and Social Council (document E/1998, pages 7-8).

For this reason, in any revision of the existing agreements, conventions and protocols on narcotic drugs, consideration must be given to inclusion of some simple and effective machinery for bringing new narcotic drugs under control, as provided for in the international treaties on narcotic drugs which are now in force.

For this reason, in the course of consolidating into a single instrument and revising the existing international conventions on narcotic drugs, referred to hereinabove, the Secretariat of the United Nations has prepared a "Draft of the Single Convention"[8] in which the machinery for bringing new narcotic drugs under international control is simplified and made more effective and flexible. The proposed draft of a single convention would vest in the United Nations Commission on Narcotic Drugs the authority of deciding, by a simple majority, to place a new narcotic drug under international control.[9] The decision would be binding on each State Party to the proposed single convention, upon expiry of sixty days after receipt of a notification that the applicable provisions of the proposed single convention are satisfied, and of a copy of the Commission's decision.[10] It is, however, also provided that a State shall not be bound by such a decision, if it files with the Secretariat a notice of rejection within the period of sixty days.[11] In this event, the State rejecting such decision "shall nevertheless be bound to observe the provisions of the (proposed single) convention in respect of the export of such a drug to a Party which shall not have rejected the said decision, or to a State not bound by said decision which shall have furnished estimates for the drug in question".[12]

Besides, the decision of the Commission on Narcotic Drugs bringing a new narcotic drug under control may be modified, or set aside, by the Economic and Social Council.[13] The validity of any decision of the Commission bringing a new narcotic drug under control may also be made subject to approval by the Economic and Social Council, if the Commission so chooses; or by the General Assembly, if the Council decides to do so.[14]

In reaching a decision which has to do with the medical or pharmaceutical properties of a drug, the Commission would be bound to consult the World Health Organization or its Expert Committee.[15]

[8] See document E/CN.7/AC.3/3. This work was authorized by the Economic and Social Council in resolution 246 D (IX) of 6 July 1949 at the recommendation of the Commission on Narcotic Drugs at its fourth session (E/1361; E/CN.7/186, annex B, sec. 15 (4).)

[9] *Idem*, section 2.

[10] *Idem*, section 3 (3), and section 12 (3).

[11] *Idem*, section 3 (3).

[12] *Idem*, section 35 (2).

[13] *Idem*, section 12 (1 a).

[14] *Idem*, section 12 (1 b and c).

[15] *Idem*, section 12 (2).

The Changes Experienced by the Narcotics Monopoly in Turkey

By Dr. Alaettin Akçasu

In this article, Dr. Alaettin Akçasu, who works in the Department of Pharmacology, under Ord. Prof. Dr. Sedat Tavat, Faculty of Istanbul, relates how the narcotics monopoly in Turkey has been strengthened over the years, so as to eliminate almost completely all possibility of misuse.

Until 1933 the cultivation of the opium poppy, the manufacture of raw opium and the internal and external trade in morphine and other alkaloids obtained from opium were not subjected to any control within the frontiers of Turkey. Until then, anyone could grow any quantity of poppy anywhere he wished, and sell his crop to any dealer at any price. In Anatolia the extraction of oil from the poppy seed was preferred to the trade in raw opium for here poppy oil held an important place as a food product.

The conventions signed at The Hague (23 January 1912) and Geneva (12 February 1925) reduced the poppy cultivation within the frontiers of the countries Parties to the conventions and placed their opium exports under close control, therefore in these countries where cultivation of the poppy was free, production increased immediately and trade in opium became a source of considerable profit. The arrival in Turkey of immigrants from Yugoslavia who specialized in this crop also contributed to the increase in production.

The Government of the Turkish Republic fully recognized the harm done to humanity by the free production of and trade in opium, and despite the fact that it was a rich source of foreign currency, on 26 January 1933 it passed law No. 2108 for the signature of the conventions of 1912, 1925 and 1931.

These conventions bound those countries that had no law for the enforcement, within their frontiers, of the control of these substances, to pass such a law within the shortest possible time. For this reason, the Government of the Turkish Republic passed law No. 2313, on the restriction of poppy growing and the control of the exportation and importation of raw opium and its derivatives. This law entered into force on 24 June 1933. Poppy growing and the trade in raw opium was thus placed under State monopoly within the Turkish frontiers. Since that date, districts where the poppy is cultivated have been restricted. These districts have been selected from among those where the poppy is a staple crop, where the best opium is produced and which are the most unsuitable for smuggling purposes. Persons intending to grow poppies are bound to declare the exact amount they wish to sow, and can only sell the opium produced to an official department, authorized to buy on behalf of the Government, or to merchants with special licences for internal trade. These dealers can only export such quantities and to such countries as are permitted.

Under a law passed in 1935 the production and sale of opium became a State monopoly, but none of the restricting clauses contained in the previous law were changed.

On 24 June 1938, the Office of Soil Products was set up under law No. 3491. This law invested the Office with the control of other agricultural products in addition to the control over the production of and

Building of Turkish National Monopoly.

Field of opium poppies

trade in opium and the production, exportation and importation of alkaloids obtained from opium, and declared the internal trade in raw opium free.

In accordance with this law, the producer could, without any restriction of time, sell his raw opium to the Office or to the merchants. The Office itself was not obliged to buy more opium than it could export. Thus the surplus product remained with the producer or the merchant, making smuggling all the easier. The only condition imposed on the dealers (in the internal trade) was that they must not up to that date have been the object of any prosecution for smuggling, and they were required to make a declaration to that effect.

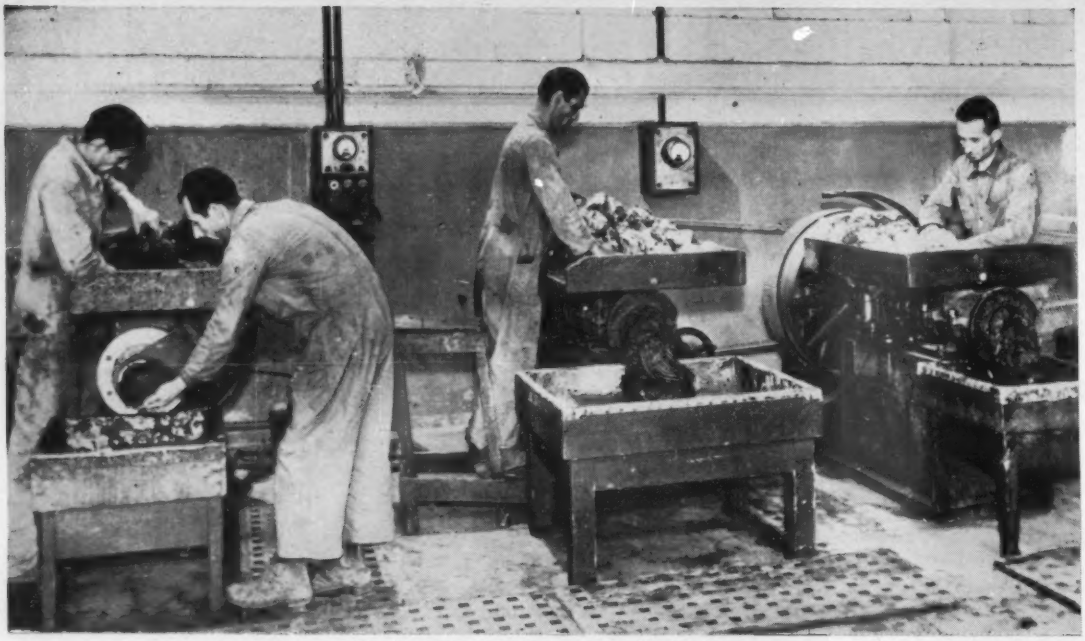
This law was applied without any modification until 1950. "In spite of the vigilance of the Customs and enforcement officers, it has been ascertained that certain evil-minded persons taking advantage of the last paragraph of the clause 6 of law No. 3491 (that the trade in raw opium is free inside the country) have been able to send freely and without any fear of control, raw opium of better quality as far as the frontiers of countries where it could be sold at higher prices, and have found opportunities to send this opium past the border. This statement has been supported by complaints received from the outside at different times."[1]

In view of the above, law No. 5621 was passed on 23 March 1950, amending clause 6 of law No. 3491 and prohibiting free trade in opium inside the country. The producer was obliged to deliver his entire production of opium to the Board, or to an office authorized to buy in the name of the Board, up to the end of August of the same year.

This law remained in force for one year, after which, owing to changes in the economic system, trade in opium was again made free inside the country. It is for this reason that clause 6 of law No. 5621 was again amended on 18 April 1951, by another law (No. 5759), and the last paragraph of the above-mentioned clause stipulated that trade in opium was free inside the country but only within the district limits. This gave greater facilities to the producer, but it also made smuggling easier, and in order to prevent this, the penalties were increased. For example, clause 27 of law No. 5621 passed on 23 March 1950, fixed a fine of £T.15 for every decare[2] of poppy plantation outside the authorized areas, and of £T.30 if the poppies were slit. In the later law, these penalties were doubled. Another clause of the law passed on 23 March 1950 provides that any person who fails up to the end of August of the same year to deliver his opium to the Office or to an organization acting in its name,

[1] From the report on law No. 5621 on the need for amending some clauses of the law respecting the Office of Soil Products and the addition of a temporary clause.

[2] About a fourth (1/4) of an acre.



Crushing raw opium into standardized opium.

Processing and stamping of raw standardized opium.

or who after this date keeps such opium on his property or in any other place, or who tries to sell or transfer such opium in any other way to any person or body other than the Office above-mentioned, or an organization acting in its name, or who takes delivery of opium whether buying it or not, and conceals it, carries it or keeps it in any place whatsoever, or helps any other person or body to transfer such opium, will be deemed to be a smuggler. The penalty is a heavy fine in proportion to the amount of opium in question, and the opium will be seized and confiscated. Whereas, the same clause of the law passed on 18 April 1951 and amended lays down that if any person does not as stipulated by clause 6 deliver the raw opium he has produced up to the end of September, to the Office of Soil Products or to the organization acting in its name in the district, such raw opium produced or gathered from the producers will be confiscated. Furthermore, the producer will have to pay a fine based on the value of the raw opium, and the dealer a fine equivalent to twice such value, as a heavy penalty. If the raw opium produced or gathered from the producers has been concealed or smuggled, the penalty as laid down in the first paragraph is imposed whether it can be recovered or not. The law applied at present requires the producer to sell his product either directly to the Office of Soil Products or to an organization authorized to buy on behalf of the Office, or directly to dealers having a trade licence from the Government.

Dealers and producers must deliver all opium in their possession to the Office in the district not later than the end of September of the same year. The producer must also submit to the Government a declaration of the quantity of opium sold, not later than three days after the sale, so as to prevent any opium from being smuggled by the dealer. This declaration is essential for any sale, and the dealer concerned is required to submit it to the Board when he delivers the opium. The penalty for any person who fails to conform with this requirement is laid down in the first part of paragraph B of clause 27 of the above-mentioned law, which states that: "If any person sells or buys without a licence or transfer, conceals, transports, carries or keeps in any place raw opium, or participates in these acts, he shall be liable to imprisonment for not less than 3 months nor more than 1 year, and a heavy fine of not less than £T 50 nor more than £T 500. The opium shall be confiscated."

The Office of Soil Products is not only in charge of the control of the sale of opium, it also controls, in collaboration with the Ministry of Agriculture, the improvement of poppy growing and the production of opium, analyses the opium for sale, supervises the purification of the opium that has been bought, and provides for the standardization of opium. Also, in agreement with the Ministries of Economy and Trade, it sets up any plant or organization that may be needed.

Every year, the Office, in collaboration with the Ministries of Economy, Trade and Agriculture, and taking into consideration the agricultural and economic possibilities and the prospects for exportation, determines the regions where the poppy is to be grown and the persons to whom permission to gather opium will be granted. After submission for approval to the Council of Ministers, these particulars are made known not later than 1 July.

The Narcotics Monopoly, which has been turned over to the Office of Soil Products, controls, in addition to opium and its alkaloids, cocaine and similar substances, hashish and habit-forming synthetic narcotic drugs.

The Effects on the Cat of Addictive Morphine Derivatives and Synthetic Drugs (Mayor's Law)

By Sermet Akad, M.D.

Dr. Sermet Akad, of the Medical Faculty of the Institute of Pharmacology, Istanbul University, explores in this article a method for determining in advance whether any narcotic is habit-producing. On the basis of Mayor's Law, he proposes to demonstrate that any narcotic inducing madness in the cat is also liable to cause drug addiction in man.

The habit-forming effects of opium, the oldest of all pain-relieving drugs, and of its main alkaloid, have been known for a long time. It is on account of this drawback that these substances cannot be freely used in medical practice. The harmful effects produced by the continual use of morphine can be summed up as follows:

1. Morphine confers on the patient a euphoria which arouses the desire for continual use of this drug. Thus habituation and addiction are the results.

2. The continued use of the drug makes it necessary for the subject to increase the doses in order to obtain the same effect (tolerance). When a person has arrived at that state he can, without any danger, absorb quantities of this drug far in excess of the dose which would be lethal to a person not habituated.

3. After a certain time, the patient reaches a condition where he must use the drug in order to carry on his normal daily activities (physical dependence).

4. The sudden suppression of the drug at this period causes severe symptoms (withdrawal symptoms).

5. Continued use of the drug causes psychic as well as physical troubles.

One of the principal aims of research in new synthetic analgesics is to produce a substance capable of being used continually without causing addiction. The need for a practical method for the study of every new drug from that point of view is obvious. It is beyond doubt that the most reliable method for such a purpose is extensive clinical application. Nevertheless, the first tests must certainly be limited to animals.

Many authors believe that the addiction liability of a drug can be determined by studying the development of tolerance to some of the effects of the drug in animals. Joel and Ettinger, for example, have studied the development of tolerance to the analgesic and the narcotic effects of morphine. A rat that is tolerant to the narcotic effect of morphine is also tolerant to the narcotic effect of eucodal, dicodid and codein (cross-tolerance).

Seevers, Collins and Tatum have shown that rats become tolerant to the narcotic effect of morphine, but not to its exciting effect, and that tolerance to two different actions of morphine, such as the narcotic and analgesic effects, occurred at different speeds.

Lewis has shown that after daily injections of 1 mg. Win 1539, rats developed tolerance to its narcotic, sedative and hyperglycemic effects, but not to its hyperthermic and bradycardic effects.

Lewis has also shown that cross-tolerance to analgesic effects against given thermal stimuli did not develop in dogs, between morphine and ketobemidon. But later on, Isbell proved ketobemidon to be far more effective than morphine in the treatment of morphine withdrawal symptoms.

These, as well as Ettinger's experiments, where codein is found to have properties similar to morphine, show that the development of tolerance to some effects, such as the narcotic or analgesic effects, are not sufficient to prove that a drug is habit-forming. Furthermore, it is known that drugs such as atropin given continually in large quantities produce tolerance but not addiction when the development of withdrawal symptoms has been studied for the purpose of detect-

ing the habit-forming capacity of a drug. Lewis, Himmelsbach, Gerlach and Stanton, Isbell, Scott, have in their experiments on various animals observed various degrees and forms of withdrawal symptoms. But Wood, Wyngaarden and Seevers state that withdrawal symptoms were not seen in Rhesus monkeys after methadon. Gross and Meier have found that ketobemidon produces withdrawal symptoms in dogs less severe than morphine, this being the reverse of what Isbell had observed in men.

As evidenced by all these experiments, the withdrawal symptoms in animals are too uncertain and irregular, and as proved by Isbell, too closely related to the dosage and duration of the administration of the drug, and to the number of times per day the drug is given. This too, shows that this method requires a rather long time, and that its results are not altogether reliable.

In this respect, the most trustworthy results are obtained from clinical experiments. Lately, Isbell experimented with a series of new synthetic drugs derived from meperidin, namely, bemidon, ketobemidon, NU-1196, NU-1179, and NU-1932. These drugs produced euphoria and relieved withdrawal symptoms of morphine. The most potent of these drugs has been found to be ketobemidon, which is even more potent than morphine and can, at the same time, produce tolerance and addiction, causing the severest forms of withdrawal symptoms.

Lewis in his experiments on animals, found isomethadon less potent in developing tolerance or addiction than methadon or morphine, whereas Finniger has proved that methadon develops tolerance to its hyperglycemic effect in rats, and Weckler and Frank, to its sedative, analgesic and hypothermic effects in dogs. Schwaiger and Boeck, through their clinical observations, claim that methadon does not develop tolerance and addiction, and that no withdrawal symptoms are seen when the drug is withheld.

Troxill, also relying on clinical observation, claims that methadon could produce tolerance, and could be given instead of morphine to morphine addicts. Hewer and Keele state that methadon can produce euphoria to the same degree as morphine. Isbell has shown that methadon can relieve the withdrawal symptoms of morphine addicts, and also if given long enough, produce weak withdrawal symptoms, once it has been withheld. Later on, Isbell and Windler have shown the development of tolerance in men to its sedative action, as well as its effects upon the pupils and respiration. They have also noted full withdrawal symptoms by discontinuing the drug in men, as well as in animals. Morphine or methadon were found to relieve those symptoms. Leufeld too, observed tolerance formation to the analgesic effect of methadon.

Today, with chemists hard at work to produce new synthetic analgesics, the need for a quick and sure method to detect a probable habit-forming potential in these new products is obvious.

The mad-cat method discovered by Mayor, nearly forty years ago, for the purpose of detecting the habit-forming capacity of analgesics in men, has not been mentioned in the medical literature of this last decade. This method, which gives in a very short time results completely in accordance with clinical observation, seems to be nearly forgotten. Mayor used this method to detect addiction liability in opium alkaloids and their derivatives. Thus, an alkaloid which, when injected subcutaneously in a cat, makes it mad, is known to have addiction liability for men, whereas the alkaloids that do not act thus are known to have no such liability. Thus morphine, heroine, dicodid, dilaudid and eucodal make a cat mad, and codein and dionin do not.

Following a subcutaneous injection of 0.0008 gr. per kg. of morphine, a cat shows a maximum dilatation of its pupils and quickening of its respiration; it moans without interruption, climbs the walls of its cage, throws itself down, heedless to pain. It shows no interest in its surroundings; a mouse, a dog or another cat awake no interest. It neither eats nor drinks. It may jump and fall down from high places. It appears to be suffering from hallucinations. A few hours later, these symptoms disappear and it becomes normal again. If during this madness, large doses such as 15-20 mg./kg. are given from time to time, the cat deveolps tonic and clonic convulsions. Morphine never puts a cat to sleep.

Joel and Fritz Arndt have shown that in a cat the cortex of whose brain has been removed, morphine only causes tonic and clonic convulsions. They also state that morphine injected in cats at the dose of 0.1-0.2 mg./kg. will induce sleep. We have never been able to induce sleep in cats with these doses; they were only calmed. In 1942, Akil Muhtar Ozden used this test with dolantin and found that it induced madness in the cat. This caused him to think that dolantin could be habit-forming. This was subsequently proved by extensive clinical observations.

In our experiments with this method, we first investigated the actions of the opium alkaloids. The results are given below.

Morphine: The injection of 8 mg./kg. always produces the picture described above. With smaller doses such as 0.05/kg., the animal was seen to pass successively through states of consciousness and unconsciousness, so that it became mad at times and then was conscious again, during which period, it looked

up when called and enjoyed being caressed. When 15-20 mg./kg. were used, it sometimes fell and showed tonic and clonic convulsions. With still higher doses such as 30 mg./kg., these convulsions became continuous, and in this state the cat usually died. With small doses such as 0.1-0.2 mg./kg., the cat was quiet and depressed, showing at times clumsiness in scratching itself with its hindlegs.

Dilaudid: Usually, 1 mg./kg. is enough to produce madness, though this becomes a rule when 3 mg./kg. are used.

Dicodid: 1 mg./kg. produced madness in a cat in every case.

Eucodal: 4 mg./kg. produced madness, but often of shorter duration. The results of these experiments are summarized in the table below:

Weight of the cat (grammes)	*Sex*	*Drug used*	*Dose mg./kg.*	*Total dose*	*Pupils*	*Observations*
1,300	F	Morphine	0.2	0.66	Moderate mydriasis	Cat sat calmly, was rather sluggish and perfectly conscious.
1,500	M	"	0.1	0.15	" "	Sluggish and calm. Showed clumsiness in the use of its hindlegs, but was awake and conscious.
2,000	M	"	0.2	0.4	" "	"
2,500	M	"	0.2	0.5	" "	"
2,000	F	"	1	2	" "	Seemed calm but presented exaggerated reflexes.
2,200	M	"	2	4.4	" "	"
2,650	M	"	5	13.25	Pronounced mydriasis	Became mad but showed periods of consciousness.
3,000	F	"	5	15	" "	"
1,700	M	"	8	13.6	" "	Complete madness.
2,200	M	"	8	17.6	" "	"
2,400	M	"	12	20.8	" "	Complete madness with periods of convulsion.
2,200	M	"	15	33	" "	"
2,400	F	"	20	48	" "	"
3,300	M	"	30	99	" "	Half an hour's madness followed by a fall with tonic and clonic convulsions. Was normal the next morning.
2,000	M	"	30	60	" "	Half an hour's madness followed by convulsions. Died an hour later.
1,800	F	Heroin	1	1.8	Moderate mydriasis	Cat showed hyper-irritability but no madness.
2,100	F	"	1	2.1	Pronounced mydriasis	Showed a few periods of madness from time to time.
1,800	M	"	2	3.6	" "	Slight periods of madness from time to time.
1,750	F	"	2	3.5	" "	Madness.
2,200	F	"	3	6.6	" "	"
2,000	F	"	4	8	" "	"
3,100	F	Dilaudid	1	3.1	Moderate mydriasis	The cat was irritable but not mad.
2,500	M	"	1	2.5	Pronounced mydriasis	Slight periods of madness from time to time.
2,200	F	"	2	4.4	" "	"
2,200	M	"	2	4.4	" "	Madness.
2,400	F	"	3	7.2	" "	"
1,500	M	Eucodal	1	1.5	Moderate mydriasis	Nothing important seen.
2,200	F	"	2	4.4	" "	Showed hyper-irritability.
2,100	F	"	4	8.4	" "	Alternate periods of madness and consciousness.
2,200	M	"	5	11	Pronounced mydriasis	Complete madness.
2,000	M	"	5	10	" "	"
2,800	M	Dicodid	5	14	" "	Alternate periods of madness and consciousness.
2,200	M	"	10	22	" "	Complete madness.
2,100	F	"	10	21	" "	"
2,000	F	"	5	10	" "	"

One may see from our experiments that these drugs, long known for their habit-forming capacity, all cause madness in cats. Likewise, experiments with dionin and codeinum phosphate never caused madness in the cat. Smaller doses produced hyper-irritability, exaggerated reflexes and mydriasis, whereas higher doses caused convulsions which were mostly tonic, opisthotonos and death.

Weight of the cat (grammes)	*Sex*	*Drug used*	*Dose mg./kg.*	*Total dose*	*Pupils*	*Observations*
2,100	M	Dionin	20	42	Moderate mydriasis	Cat was fretful, enjoyed being caressed, and presented exaggerated reflexes.
2,000	M	"	30	60	" "	Highly irritable. Showed tremor of ears and body when frightened. Exaggerated reflexes.
1,800	F	"	40	72	Pronounced mydriasis	Generalized tonic convulsions and opisthotonos; showed periods of relaxation followed again by convulsions. Unconscious even in these periods. Died in four hours.
1,700	M	Dionin	80	136	Pronounced mydriasis	Same as above. Died in two hours.
1,650	M	"	80	120	" "	Opisthotonos, tonic and rarely clonic convulsions followed a short period of irritability. Showed periods of relaxation during which it tried unsuccessfully to get up. Died in three hours during convulsions.
2,000	F	Codeinum phosphate	40	80	Moderate mydriasis	The cat was irritable, easily frightened, and presented exaggerated reflexes.
2,100	M	"	60	126	" "	"
1,800	M	"	80	144	Pronounced mydriasis	Irritated, frightened, showing exaggerated reflexes. Showed periods of opisthotonos and convulsions between which it was conscious.
2,000	M	"	120	240	" "	Same as above. Died in four hours.
2,200	F	"	150	330	" "	Half an hour's irritability followed by opisthotonos, tonic and rarely clonic convulsions. Recovered the next morning.
2,600	M	"	200	520	" "	Same as above, but died in three hours.
3,000	M	"	300	900	" "	Died in two hours during tonic convulsions and opisthotonos.

These results are concordant with the clinical observations. It is generally recognized that codein and dionin are not habit-forming for humans.

We performed another series of experiments in which the drug used was dolantin. Dolantin injected subcutaneously in a cat in quantities of 5-10 mg./kg. produces torpor. The use of 20-25 mg./kg. induces sleep in cats, but madness and periods of tonic convulsions and opisthotonos are seen with the use of 40 mg./kg.

The results of our experiments with dolantin are given below:

Weight of the cat (grammes)	*Sex*	*Drug used*	*Dose mg./kg.*	*Total dose*	*Pupils*	*Observations*
2,700	M	Dolantin	5	13.5	Moderate mydriasis	The cat was calm and sluggish.
2,000	M	"	10	22	" "	"
1,800	F	"	20	36	Pronounced mydriasis	First fretful, then stunned, then slept.
2,200	F	"	25	50	" "	"
2,100	M	"	40	84	" "	Became mad in half an hour. Showed periods of opisthotonos and clonic and tonic convulsions during which it breathed haltingly and was unconscious. Started reacting when called, one hour later. Four hours later, all the symptoms except mydriasis had disappeared.
1,650	M	"	20	32	" "	Seemed stunned. Became mad with a second dose of 20 mg. given half a hour later. Returned to normal in three hours.
1,500	M	"	35	52	" "	Became mad, showing periods of opisthotonos and convulsions.

The madness produced is the same as in the case of morphine. The cat moves about incessantly in an unconscious way. It climbs the walls of its cage, hitting and even injuring itself. It shows no interest for its surroundings and seems to be suffering hallucinations as if it had visions. Respiration is rapid. The cat neither eats nor drinks. It is not frightened by anything. Its pupils are mydriatic. These experiments show that dolantin can induce madness in a cat, which is in accordance with its habit-forming potential in humans.

We experimented finally with methadon. When 5-10 mg. of methadon is injected into a cat, it produces madness as in the case of morphine. This shows that methadon may produce addiction in men, this is in accordance with the experiments on animals described before, and with numerous clinical observations. The results of our experiments are given below:

Weight of the cat (grammes)	*Sex*	*Drug used*	*Dose mg./kg.*	*Total dose*	*Pupils*	*Observations*
1,750	M	Polamidon	3	5.25	Moderate mydriasis	The cat showed some excitement after lying quietly for an hour.
3,400	F	"	1	3.4	" "	Was quieter.
3,400	M	Polamidon	5	17	Pronounced mydriasis	Showed alternate periods of madness and quietness during which it was conscious.
1,800	M	"	7	12.6	" "	"
1,750	M	"	12.5	22	" "	Became completely mad, showing periods of opisthotonos and convulsions. Later on, it spread itself out on its belly paralysed, with its fore and hind legs lying flat apart. Respiration was very rapid. It had recovered by the next morning.
1,600	M	"	6	9.6	" "	Became completely mad and recovered slowly in four to five hours.
2,000	F	"	8	16	" "	"

Experiments with pethidin and methadon on rabbits showed that smaller doses produced sluggishness in some, and sleep in others. Larger doses were seen to cause death with convulsions. On dogs, these drugs caused sluggishness. Therefore, not only were the effects of these drugs on cats similar to those of morphine, but also their effects on other animals were the same.

In another series of experiments which we performed with amphetamin, we never succeeded in causing madness. Large doses resulted in tonic and clonic convulsions, while still larger doses caused death. This proves that the cat experiment can only be used to discover the habit-forming capacities of morphine-like analgesics.

Experiments with persedon, a new hypnotic, never resulted in madness. The action of persedon on the cat can be seen below:

Weight of the cat (grammes)	*Sex*	*Drug used*	*Dose mg./kg.*	*Total dose*	*Pupils*	*Observations*
1,750	M	Persedon	30	52.5	Mydriasis	The cat showed little movement, was sluggish, had difficulties in scratching itself, ate when given food.
2,700	M	"	50	135	Pronounced	Sat quietly.
3,250	M	"	50	172.5	—	"
1,500	M	"	60	60	—	Showed quarrelsome temper, clumsiness, ate when given food.
2,650	M	"	75	198	Moderate	Showed exaggerated reflexes, staggered about clumsily.
1,750	F	"	100	175	Pronounced	Slept.
1,900	F	"	100	190	Moderate	Slept; showed exaggerated reflexes.
1,600	M	"	150	240	—	Slept after half an hour. Exaggerated reflexes.
1,700	M	"	200	340	Pronounced	Slept after half an hour; exaggerated reflexes. Had slight clonic convulsions that lasted for hours. Woke up the next day.

It can be seen from these experiments that the cat test first proposed by Mayor for opium alkaloids, helps to detect the habit-forming potential not only in opium alkaloids, but also in synthetic analgesic substances showing morphine-like actions as well.

This method is simple to use and gives in a few hours wholly reliable results.

In view of the considerable work done by chemists in producing new synthetic analgesics of different types and formulae, we think it very important to have a method that would show rapidly the habit-forming possibilities of these new drugs. We believe that the cat method is very useful for this purpose and hope that it may be of some advantage in helping chemists and pharmacologists in the search for analgesics free of such harmful effects.

The Story of "Porphyroxine-Meconidine"

(The red-turning alkaloid of opium)

"Porphyroxine-meconidine" is the most mysterious of the opium alkaloids, but in recent years its true analytical properties have been learned. Its percentage in opium is quite small, but in trying to determine the origin of illicit opium by scientific means, it is of value. Its colorimetric determination gives a very helpful indication of origin, especially for differentiating between Indian and Iranian opiums.

More than one hundred years ago it was discovered that opium contains an alkaloid characterized by the property of changing to a red-coloured compound when heated in dilute mineral acid; but this alkaloid is still rather mysterious. Even its elementary formula is not known. In the lists of opium alkaloids it often appears three times, once under a name, rhoeadine, belonging to another alkaloid of a different species of poppy, and under two other names, "porphyroxine" and "meconidine", with two completely different descriptions, both incorrect. It has also been known under the name "opine". At least five chemists, prior to 1947, claimed to have isolated it, but without having really accomplished the isolation. The descriptions they gave of its properties apparently apply to different bases; are inconsistent with each other; and have generally been unverifiable by others, except as to the red-turning property.

In the last four years new researches have discovered no evidence for more than one red-turning alkaloid in opium; it is the same in all types of opium though varying greatly in amount; and its analytical properties have now been fairly well determined. It has been isolated (1947), but not in sufficient quantity for determination of its chemical constitution. It seems best, in view of the past mistakes, to wait until this is done before fixing upon a final name which will be associated with a true description. In the meantime, the red-turning alkaloid will sometimes be referred to as "porphyroxine-meconidine"; the hyphenated name indicating that just one alkaloid is meant, which has been known under the names "porphyroxine" and "meconidine"; while the quotation marks are used because the descriptions under these names do not entirely correspond to the real alkaloid, and, in fact, neither "porphyroxine" nor "meconidine", as previously separated and described (before 1947), has any real existence as a correctly described, individual alkaloid.

Merck's Discovery

The red-turning alkaloid was discovered by E. Merck in 1837 in Bengal opium, and named "porphyroxine".[1, 2*] He mentioned that he also found it in Smyrna (Turkish) opium. Thebaine had been discovered only two years before; morphine, narcotine, codeine, narceine, and pseudomorphine were also known at the time, and the non-basic substances meconin and meconic acid. Pseudomorphine is an oxidation product of morphine and probably not a natural alkaloid of poppy juice. If narceine is counted as one of the major opium alkaloids — it is usually sixth in amount — then porphyroxine was the first of the natural minor alkaloids of opium to be discovered. It is ironical that there is still so little known about it.

In 1837 quite a number of opium alkaloids were still undiscovered. Of these, at least papaverine and cryptopine, and probably laudanine and one or two others, normally exceed the red-turning alkaloid in amount.

Merck gave the following analysis for his sample of Bengal opium in parts per 100: 8 morphine, 5 narcotine, 0.5 codeine, 1.0 thebaine, traces of meconin, 0.5 porphyroxine.

The porphyroxine, precipitated with thebaine by ammonia, and separated by crystallizing the thebaine from ether, which left the porphyroxine as a resinous mass, was certainly anything but a pure substance. The pure red-turning alkaloid probably does not exceed 0.1 per cent in the usual Indian opium, though possibly it may sometimes be as high as 0.2 per cent. Although Merck stated that it crystallized in fine glistening

* Superior figures in the text indicate reference to the bibliographic notes at the end of this article.

needles, this was probably a partial crystallizing out of some other substance, and Merck himself concluded:

"When, as I hope, I succeed in obtaining this substance pure enough, that the elementary analysis can be undertaken, and when it has been confirmed thereby as a new constituent of opium, then I propose to name it porphyroxine (from purple and acid)."[1]

Merck said that the new substance "is neither basic nor acid" — he did not say that it was an alkaloid, but this seems to have soon become the accepted idea.

Apparently, the time never came that the elementary analysis was determined, but nevertheless, porphyroxine was generally accepted as a constituent of opium during the next thirty years. Chemists writing about opium sometimes referred to it, and there were several articles about it, which are now very hard to track down.

Merck was responsible for another small item, relating to the use of the red-turning property of porphyroxine as a test for the presence of opium in forensic cases.[3]

Riegel gave a different and apparently inconsistent method of separating porphyroxine from opium; it was extracted by ether with narcotine, and then separated.[4] Riegel also claimed a crystalline product, but did not give the elementary formula or any other additional information about chemical properties.

The foregoing researches were included by J. J. Berzelius in his *Lehrbuch der Chemie*, 1848, and were, therefore, well known to chemists of the time. Berzelius disliked the name "porphyroxine", and proposed the name "opine". He classed it among the organic bases.[5]

In 1852, an article by Robertson concerned chiefly the use of "porphyroxine" or "opine" in forensic cases to show the presence of opium, without adding any important information on chemical properties.[6]

Porphyroxine was included in at least three studies of the pharmacological properties of opium alkaloids, by Albers, Fronmüller, and Baxt.[7, 8, 9] Albers and Fronmüller, it seems, both used porphyroxine supplied by Merck. No new information concerning the isolation of the alkaloid or its chemical properties was provided.

Hesse's Meconidine

The situation was changed completely by the researches of Hesse, which did so much to elucidate the composition of opium, but nevertheless, as far as the red-turning alkaloid was concerned, came nearer confusing the few facts that were already known.

Hesse discovered rhoeadine in *Papaver rhoeas* in 1865,[10] and soon afterwards published two articles about it.[11, 12] *Papaver rhoeas* is the common red "corn poppy" or "field poppy" of Europe. In cultivation for floral purposes it has numerous colour varieties, of which the Shirley poppies are especially well known.

In 1866 Hesse discovered or verified that opium contains a red-turning alkaloid, and at once jumped to the conclusion that it was rhoeadine.[11] He did not say anything about previous knowledge of porphyroxine except to refer slightingly to Merck's discovery as follows: "Merck noted this coloration a long time ago, without being able to prepare the reactive substance; for the porphyroxine, as he called it, contained less than 1 per cent of rhoeadine."

Since the red-turning substance in opium is not rhoeadine, Hesse's remark about its percentage in Merck's porphyroxine was merely an incorrect guess. However, this is the insecure foundation of the idea that opium contains rhoeadine. Even recently, commentators have said that Hesse "found rhoeadine" in Merck's porphyroxine!

Three years later (1869), Hesse acknowledged that opium does not contain rhoeadine, but a different alkaloid.[12] In the next year, 1870, he published his account of "meconidine", as he renamed the red-turning alkaloid.[13]

Hesse's meconidine was never obtained crystalline, nor were any of its salts, and undoubtedly it was merely a mixture of phenolic or acidic alkaloids. The preliminary partial purification of the bases that Hesse then investigated included their extraction by dilute acetic acid from chloroform, a process that may well have involved the loss of a large part of these bases, especially of the red-turning alkaloid. At any rate, he obtained a more or less purified solution of bases dissolved in KOH, containing codeine and the bases he named meconidine, codamine, laudanine, and "Base X".

The codeine was removed by shaking out the alkaline solution three times with ether; "it goes over into ether much quicker than the other four bases" — from alkali, at any rate. The bases were then freed from alkali combination with NH_4Cl and obtained in etheral solution. With slow evaporation of the ether, laudanine first crystallized out. On further concentration, an amorphous deposit was obtained. On addition of some fresh ether, washing with aqueous solution of $NaHCO_3$, and further spontaneous evaporation, crystalline codamine was obtained. As soon as an increase of these crystals was not noted any more, the bases remaining in the ether were transferred to solution in dilute acetic acid, and this aqueous solution then saturated with NaCl. A resinous precipitate formed, which according to Hesse was meconidine hydrochloride. "Base X" remained in solution; apparently no further information about this base was ever

given; presumably it is an "undiscovered" phenolic alkaloid. The meconidine hydrochloride remained non-crystalline even after several re-solutions with dilute acetic acid and re-precipitations with sodium chloride had freed it completely, according to Hesse, from traces of "Base X". The "pure salt" was dissolved in water, $NaHCO_3$ added, the alkaloid extracted with ether, and the etheral solution filtered with some purified animal charcoal. Still the free base did not crystallize, either.

Hesse purified codamine from adherent meconidine by dissolving the crystals in dilute sulphuric acid and boiling, to convert the meconidine to the red compound, and then treating with animal charcoal to decolorize the solution, from which the codamine could then be recovered. After boiling some of the meconidine itself in dilute sulphuric acid, Hesse reported that "animal charcoal takes the changed substance out of a neutralized solution very readily, and then the solution contains no organic base any more". This seems to be what he relied on to classify meconidine as an isolated individual base.

In this article Hesse acknowledged that "meconidine agrees with rhoeadine only in small points". Concerning Merck's porphyroxine he now said, "This coloration was first observed by Merck, who was, however, unsuccessful in isolating the reactive substance, for the *porphyroxine*, which Merck described as the red-colouring opium substance, is a mixture of several bases, among which is meconidine, as I call the substance. One can easily be persuaded of the heterogeneous character of porphyroxine if one subjects it to the same analytical treatment as I describe for the ether extract of opium solution." Undoubtedly Merck's porphyroxine *was* a mixture, but it does not appear that Hesse ever actually analysed it, or any mixture obtained by following Merck's directions, although his remarks have sometimes been referred to in that sense.

In 1881 a brief article by Dey discussed again the use of the porphyroxine colour reaction as a test for opium in forensic chemistry.[14] Dey was working in India, and while he did not specifically recommend the test for the purpose of distinguishing Indian opium from Turkish, he remarked incidentally, "This constituent is not present in Turkey and Smyrna opium", and "If Turkey opium is employed for poisoning no porphyroxine can be found". This of course is incorrect; but, as the Secretariat chemists have observed, Indian opium does usually contain a great deal more "porphyroxine-meconidine" than other kinds, so it is possible to make the test in such a way that *generally*, only Indian opium would respond. The clearest distinction, however, is between Indian and Iranian opiums. The opium from certain districts in Turkey (Zile and Malatya) is likely to contain as much "porphyroxine-meconidine" as even the highest in Indian opiums.

A brief note in 1930, by Bamford, corrected Dey's observations to the extent of noting that Turkish opium does give the test.[15]

Rakshit's Porphyroxine

In 1919, Rakshit published his account of the isolation of porphyroxine.[16] This was the most detailed thus far and convinced most readers, at first, that an alkaloid properly named "porphyroxine" had really been isolated at last. In 1926 Rakshit published an article on the chemistry of porphyroxine, in which amongst other properties described he said that it was converted to codeine by heating with hydrogen peroxide in 2 per cent KOH solution, and he assigned to it a structural formula closely related to codeine.[17]

Small later remarked that the structural formula proposed involved a "return to the improbable Pshorr formula" for codeine.[18]

To elucidate the structure, Rajagopolan attempted to obtain porphyroxine as described by Rakshit. He was not particularly interested in the red-turning property but in porphyroxine as an alkaloid closely related to codeine. All he could find in this sense was codeine itself, and he suggested that Rakshit's porphyroxine might be nothing but impure codeine.[19, 20] A further study of Rakshit's articles and some experiments by the Secretariat now make this virtually certain. This in no way disposes of the real red-turning alkaloid, which certainly exists, but its structural formula is unknown and it is not even known whether it is one of the "phenanthrene alkaloids" of opium.

As Rajagopolan pointed out, Rakshit did not even mention codeine as present in describing his method of separating porphyroxine, and so did not explain how he considered he had separated his porphyroxine from codeine — or from the other known alkaloids either, for that matter. He did say that as a matter of "striking contrast" in properties, "unlike codeine, the aqueous solution of its hydrochloride gives a white or pale yellow precipitate with ammonia".[21] This could easily be due to impurities, which, of course, included a certain amount of the real red-turning alkaloid.

Rakshit's values for codeine in typical samples of Indian opium, given in another article,[21] were only about half the amount now recognized as present,[22] as was also pointed out by Rajagopolan.[20] In this article Rakshit criticized the earlier codeine method of Annett and Sen, saying, "The authors appear to have taken no precaution to remove porphyroxine, which is always extracted to some extent by almost all immiscible solvents from the lime solution of opium and in a moderate degree by toluene." He went on to say concerning thebaine, meconidine, codamine, laudanine, protopine, and porphyroxine: "with the exception

of porphyroxine, these are only nominally present in Indian opium".[21]

Rakshit did not state the yield of his porphyroxine in giving his method of obtaining it,[16] but the foregoing quotations incontestably show that he considered it occurred well in excess of the usual minor alkaloids and that it was capable of substantially affecting the codeine determination even if only partially extracted, and that in Indian opium it even exceeded thebaine, which was only "nominally" present.

Rakshit's method was the following[16] (with comments):

Opium was triturated with freshly-slaked lime, water added, the solution obtained was filtered and the filtrate extracted with ether. The ether was dried with calcium chloride, filtered, and evaporated. A quantity of the powder so obtained was extracted five times with boiling light petroleum.

Here occurs a startling ambiguity. Those who have previously summarized the method have considered that it was continued with the residue *not* dissolved by the light petroleum;[23, 18] and this is the natural reading, but actually Rakshit does not quite say this. He only says, "finally the contents of the flask were collected, dried, and powdered". In view of the fact that the porphyroxine was later extracted with light petroleum and re-crystallized from that solvent, it seems strange to extract the alkaloidal mixture earlier with light petroleum and discard the extracts; and possibly "the contents of the flask" means the light petroleum extracts. However, if the final porphyroxine is conceded to be mainly codeine, it does not make much difference which part is used, as the codeine would be partly but certainly not completely removed in five extractions with light petroleum.

At any rate, the dried and powdered "contents of the flask" were treated with 10 per cent HCl during half an hour, then diluted with an equal volume of water added gradually during one hour, and filtered. (This hour and a half in solution in strong mineral acid can hardly be conducive to isolating the red-turning alkaloid unchanged.) The solution was then treated with $NaHCO_3$ to slight excess, and after half an hour filtered. There was no statement as to what this accomplishes; but in fact it removes a considerable part of the papaverine and thebaine present, leaving the codeine in solution. Clearly, the method as a whole primarily separates a portion of the codeine.

The remaining steps were: the filtrate was extracted four times with chloroform, the solvent evaporated, and the dried, powdered residue extracted with heated light petroleum. This on evaporation yielded pale yellow prisms, melting at 134-135°, and declared to be porphyroxine.[16]

Some experiments of the Secretariat throw further light on the process.

Since Rakshit's porphyroxine is declared to be present in the lime-water extract of opium, and to be non-phenolic and non-acidic, and somewhat soluble in light petroleum, a lime-water extraction of 5 grammes of Indian excise opium was made and the liquid extracted continuously with petroleum ether in an extraction apparatus for about five hours. The petroleum ether extract was evaporated to a small volume, whereupon, on removal from the steam bath, the larger part of the alkaloids precipitated, and were filtered off and washed with a little fresh petroleum ether. The petroleum ether solution was then evaporated and the two portions of alkaloids examined separately, with the following results:

(A) Portion more soluble in petroleum ether: 0.0993 gramme.

(B) Portion less soluble in petroleum ether: 0.1450 gramme.

	Alkaloids from A		*Alkaloids from B*	
	Weight (gramme)	*Per cent*	*Weight (gramme)*	*Per cent*
Papaverine	.0079	8.0	.0183	12.6
Thebaine	.0399	40.2	.0147	10.1
Codeine plus cryptopine	.0412	41.5	.1008	69.5
	.0890	89.7	.1338	92.2

	Total of the alkaloid in the two portions (gramme)	*Percentage of the opium*
Papaverine	.0262	0.52
Thebaine	.0546	1.09
Codeine plus cryptopine	.1420	2.84
Portion of the petroleum ether extract not accounted for by these alkaloids	.0215	0.43

The amount of red-turning alkaloid in the petroleum ether extract was insignificant in comparison with the amount in the opium used. Most of the small amount present was taken out by alkali in making the separations, a very little remained in the thebaine residues, but none with the codeine.

The larger papaverine residue and the four thebaine and codeine-cryptopine residues crystallized completely. It will be noted that the thebaine in this Indian excise opium, soluble in the lime-water solution and extractable by petroleum ether, exceeded 1 per cent (by weighing). The codeine crystallizes with one molecule of water of crystallization; the percentage of anhydrous codeine (plus cryptopine) was, therefore, about 2.67 per cent. The codeine determination on this opium by the method used by the Secretariat,[22] involving ether extraction from the lime-water solution, was

3.07 per cent anhydrous codeine, or 3.27 per cent crystalline.

In these determinations no treatment with $NaHCO_3$ was used. Another extraction of lime-water filtrate representing 6 grammes of the same opium was then made, this time with ether. The residue from the ether was treated five times with petroleum ether, which was then evaporated. In view of the ambiguity in Rakshit's method, both portions, that dissolved by petroleum ether and that remaining, were separately studied. Each was dissolved in dilute acetic acid, filtered, treated with $NaHCO_3$, and after standing for about half an hour, again filtered. The filtrates were extracted with chloroform. This solvent was evaporated and the residues examined without again extracting with petroleum ether.

Dissolved by petroleum ether and extracted from $NaHCO_3$ filtrate—.0635 gramme.

	Weight (gramme)	*Per cent of residue*	*Comparative porphyry colour obtained*
Papaverine	.0050	7.9	none
Thebaine	.0134	21.1	0.6
Codeine plus cryptopine	.0408	64.2	none
Phenolic or acidic residue from thebaine separation	.0015	2.4	5.6
	.0607	95.6	

Not dissolved by petroleum ether; extracted from $NaHCO_3$ filtrate—0.2530 gramme.

	Weight (gramme)	*Per cent of residue*	*Comparative porphyry colour obtained*
Papaverine	.0085	3.4	none
Thebaine	.0452	17.9	2.0
Codeine plus cryptopine	.1537	60.7	none
Phenolic or acidic bases:			
From papaverine extraction	.0009	0.3	1.25
From thebaine extraction	.0049	1.9	36.0
After codeine extraction[a]	.0151	6.0	0.5
	.2283	90.2	

[a] Some morphine was present, which chiefly accounts for the size of this residue, even though not all the morphine present was re-extracted.

The method of separation was briefly as follows: The mixture of alkaloids was transferred to a separatory funnel by means of CCl_4 and about 7 cc. of unbuffered dilute acetic acid solution. A wash solution of dilute acetic acid was used and the papaverine shaken out with CCl_4, the extracts shaken with alkali solution and then with three solutions of 2 per cent sulphuric acid. The papaverine was then recovered from the sulphuric acid solutions. (There was no evidence of narcotine.) The acetic acid solutions were then buffered with sodium acetate and the thebaine shaken out with CCl_4, the extracts being shaken with two portions of rather strong alkali solution and then washed with water, filtered, and evaporated. As will be seen from the figures above, practically all the red-turning alkaloid was in the CCl_4 with the thebaine, but nearly all of it was held by the alkali solutions, indicating a phenolic or acidic character for the true "porphyroxine-meconidine". The buffered acetic acid solutions were then made alkaline and the codeine and cryptopine extracted. Nearly all the cryptopine was here (also any protopine, not considered separately from cryptopine in these determinations), only traces getting into the thebaine residue. The various alkali solutions were acidified, then made ammoniacal, and extracted for the phenolic or acidic bases.

The total codeine (plus cryptopine) in the two portions was 3.24 per cent of the opium, checking almost exactly with the previous codeine determination on 2 grammes of this opium of 3.27 per cent crystalline codeine (3.07 per cent anhydrous). The total thebaine, even with the $NaHCO_3$ treatment, was 0.98 per cent. Also, it will be noted that the ratio of thebaine to the other bases present is increased by petroleum ether extraction. The total papaverine was 0.22 per cent of the opium; it is limited in amount by the use of a lime extract and by the $NaHCO_3$ treatment. Probably the proportions of thebaine and papaverine in a final product would be less by working on a larger scale, as Rakshit did, but there is nothing in his procedure to indicate that they were eliminated.

From these experiments it is clear that Rakshit's porphyroxine can only have been primarily codeine, with impurities of thebaine and papaverine and a small proportion of the real red-turning alkaloid. The thebaine impurity may well have been considerable. In fact, Rakshit states that after recrystallizing three times from petroleum, his porphyroxine gave a red colour with concentrated sulphuric acid, and orange with concentrated hydrochloric acid.[16] In the circumstances, these reactions must be attributed to thebaine, although the real "porphyroxine-meconidine" does turn red, dissolving to a brick-orange colour soon changing to brown, when treated with concentrated sulphuric acid. (Some of its other colour reactions are given later.)

In 1926 in a long article Machiguchi reported percentages for virtually all the known opium alkaloids in Japanese opium, but with very few new facts concerning them or the methods of separation.[24] He reported 0.25 per cent meconidine. Concerning porphyroxine, he said that a crystalline substance was obtained resembling Rakshit's porphyroxine and having the same melting point, but that analysis showed it to be a mixture of codamine, laudanine, and meconidine. This reflects Hesse's statement concerning Merck's porphyroxine, quoted earlier; but certainly these bases, all phenolic, could not possibly have constituted Rakshit's porphyroxine.

Isolation of "Porphyroxine-Meconidine"

In 1947 Fulton, working at the United States Bureau of Narcotics on the problem of determining the origin of seized opium by chemical and physical means, undertook the isolation of the red-turning alkaloid from approximately 2 pounds of seized Indian opium. His results were given in a short mimeographed paper which was published in 1948 in a United Nations document, having been communicated to the Commission on Narcotic Drugs by the representative of the United States of America.[25] The method of separation, not given in detail in the paper mentioned, was essentially as follows:

(1) The opium, 870 grammes, was extracted with lime-water in several portions, a total of 250 grammes $Ca(OH)_2$ and 7,500 cc. water being used. The solution was filtered.

(2) The filtrate was put in a large round-bottom flask and extracted continuously with ether for 115 hours, operative time. The ether was changed in the receiving flask several times. This extractor was not very efficient and the long extraction was necessary to get out nearly all the "porphyroxine-meconidine". Even at the end, traces of this alkaloid were still being extracted as well as some "alkaloid 5". The latter is a base, probably phenolic, that gives a thebaine-like reaction with sulphuric acid. This left in the aqueous solution most of the morphine, narceine, and the bases designated in this investigation as alkaloid 3 and alkaloid 4. The "porphyroxine-meconidine" was designated as alkaloid 1.

(3) The ether was evaporated off, and the residue of alkaloids taken up in dilute acetic acid (about 5 cc. glacial acetic acid in a total of about 140 cc. water). The solution was then buffered with 25 grammes sodium acetate and extracted continuously with carbon tetrachloride. This left in the aqueous solution practically all the morphine and alkaloid 3 that had been extracted by the ether in the preceding step, and a large part of the codeine and alkaloid 5.

(4) The phenolic alkaloids were now shaken out of the CCl_4 with NaOH solutions of gradually decreased strength (10 to 2 per cent), until all of the alkaloid 1 was in the aqueous solution, and the NaOH solutions washed with fresh CCl_4 until the non-phenolic alkaloids were removed. This is a tedious process. The "porphyroxine-meconidine" clings to the other alkaloids and it is almost impossible to remove all of it from the CCl_4 solution of non-phenolic alkaloids; however, nearly all was separated. The CCl_4 removes the codeine, thebaine, cryptopine, and papaverine. Narcotine is virtually insoluble in lime-water solution, but if any were present it would also be removed here; likewise any very minor non-phenolic alkaloids which have not been separately distinguished in these investigations; e.g., protopine, neopine, and laudanosine.

(5) The alkaloids which, although phenolic, are extractable by chloroform from alkali, were then shaken out. Since these are about the same phenolic bases that can be taken out of lime solution by a long, continuous ether extraction, very little further separation of alkaloids was accomplished, except to make sure of the complete elimination of morphine and alkaloid 3 and perhaps most of any remaining alkaloid 5, by leaving them in the aqueous alkali. Since the volume of alkali solution from the preceding step was rather large, this main solution was acidified with acetic acid, then made ammoniacal, and shaken out with chloroform; the chloroform extracts were then shaken in turn with two alkali solutions before being shaken with a dilute solution of ammonium salt and then with water. At this point the alkaloids still present in the chloroform extract, so far as found later, were the following:

Alkaloid 1 — "porphyroxine-meconidine".

Alkaloid 2 — probably laudanine.*

Alkaloid 6 — a weak base (possibly lanthopine or narcotoline?)

Alkaloid 7 — a base yielding colour reactions like those of alkaloid 3, but extractable by $CHCl_3$ from alkali.

At the time, the presence of alkaloids 6 and 7 was not known; they were discovered at a later stage.

(6) At this stage, it would probably have been best to reduce the chloroform solution to a smaller volume and shake out the alkaloids, to removal of alkaloid 1, with dilute acetic acid, leaving most of the alkaloid 6 in the chloroform. However, the desirability of this purification was not recognized at the time, and the chloroform was evaporated off. Another trial of continuous extraction by CCl_4 from buffered acetic acid solution was made on a portion of the residue but did not accomplish much separation; a hand shake-out was then decided on. The residue of bases was treated with 5 per cent acetic acid and the solution buffered with sodium acetate in the proportion of 4 grammes per 10 cc. Whitish burrs of crystals formed in the buffered solution. At the time, these were left in the process, but in any future separation on a larger scale it would doubtless be best to filter off this precipitate and at least process it separately, whether it consists mainly of alkaloid 1 or alkaloid 2. The solution was shaken out at room temperature with carbon tetrachloride, using three wash solutions of buffered acetic acid, in small volumes. The extracts were shaken with

* Some recent experiments on known laudanine, obtained by the kindness of Professor Fuchs, Head of the Pharmacognostical Institute, University of Vienna, from the Späth collection, have shown that, contrary to earlier statements, laudanine is extractable by chloroform from 2 per cent NaOH solution.

dilute ammonia and then water. The extraction was a very long process. Occasionally the wash solutions were each poured back one step and a new one added, to prevent gradually carrying the alkaloid 2 and alkaloid 7 past them. The first two portions of CCl_4 were set aside because of high content of alkaloid 6; the many additional extracts were evaporated. At this stage the alkaloid 1 crystallized readily, but it was still rather brown and not yet completely free of other alkaloids. The weight was 728 mg. Alkaloids 2 and 7 were largely left in the solutions of buffered acetic acid.

The remainder of the process as actually performed involved so many partial separations and recombinations that it is difficult to summarize, but the two chief methods of further separation will be given.

(7) A petroleum ether extraction was undertaken with the intention of freeing the base from the brown colour, but it proved to be more effective in separating the other alkaloids from the alkaloid "porphyroxine-meconidine". The residue of bases was treated with 10 per cent acetic acid until disintegrated, poured into the extraction apparatus without filtration, and made slightly ammoniacal. A fairly copious precipitate formed, which showed almost no tendency to dissolve in the petroleum ether. A two-hour extraction yielded a nearly colourless extract and a residue which contained some crystals but as a whole refused to crystallize. It was a mixture of alkaloids 1, 2, 6, and 7, while the greater part of the precipitate of alkaloid 1 remained in the extractor. At this point, it would probably have been best to continue the extraction with pure ethyl ether, or if necessary, ether-acetone. Actually, the alkaloid 1 was recovered by using successively benzene, benzene-acetone, and benzene-isopropanol; but each change of solvent brought over colouring matter also.

(8) Another method of separation was the following: The mixture of bases was dissolved in dilute acetic acid and shaken in a separatory funnel with CCl_4. This takes out alkaloid 6, but so slowly that the solvent was finally changed to chloroform. This removes alkaloid 6 readily, but also a considerable part of the alkaloid 1. Accordingly it was necessary to back-extract the chloroform with small volumes of dilute acetic acid, then to shake out with chloroform again, and again back-extract with dilute acetic acid. Finally, the acetic acid solutions were combined, made ammoniacal, and shaken out with CCl_4. The CCl_4 extracts were shaken with two small volumes of buffered acetic acid (to remove any remaining alkaloids 2 and 7), and then with a small volume of dilute ammonia, and finally with water. This yielded some isolated "porphyroxine-meconidine" nearly pure, but there are two difficulties with the procedure. First, the alkaloid 1 becomes more and more sensitive to acid as it is purified, and at this stage even the solutions in 5 per cent acetic acid begin developing the purplish red colour on standing a short time. Therefore, this extraction, as a means of removing alkaloid 6 and some colouring matter, probably should be made at an earlier stage (see step (6)). Secondly, the purified alkaloid 1 has only a slight solubility in CCl_4, and is only slowly extracted by this solvent even from an ammoniacal solution. In fact, the CCl_4 extraction was finally discontinued, and the remainder of the alkaloid extracted with chloroform. These $CHCl_3$ extracts, following the CCl_4 extractions, were not shaken with buffered acetic acid, but were washed with water and evaporated. Chloroform is a relatively good solvent for the alkaloid 1, but also extracts more impurities than does CCl_4. This extraction also yielded some isolated "porphyroxine-meconidine" fairly pure.

The two best residues of "porphyroxine-meconidine", amounting to 273 mg., melted fairly sharply at 175°. They were thought to be free of other alkaloids, but were still slightly brownish.

In other residues, containing varying amounts of alkaloids 2, 6, and 7, more alkaloid 1 was present, to a total of possibly 0.5 gramme. Allowing for losses, it still does not seem that the total amount can have exceeded 0.1 per cent of the opium (870 mg.). This opium had a comparative colour-value for "porphyroxine-meconidine" of 35. This is high, but a few samples of opium have been found even as high as 70. It seems, therefore, that this alkaloid may reach, at most, a maximum of about 0.2 per cent of the opium. The average in Indian opium would probably be somewhat under 0.1 per cent; in Turkish opium, around 0.03 per cent; in Iranian opium, little, if any, more than 0.01 per cent. (See the graph of comparative values, given later.)

Some Analytical Properties of "Porphyroxine-Meconidine"

The following account of properties is taken from Fulton's paper,[25] slightly revised. The red-turning alkaloid of opium is soluble in alkali and is presumably a phenol. It can be extracted from solutions either weakly basic or weakly acidic, by most organic solvents, but most extractions are very hard to make complete. This is partly because this alkaloid has a rather limited solubility in most solvents; in addition, separations are particularly difficult because the "porphyroxine-meconidine" seems to cling to some of the other alkaloids. Thus, carbon tetrachloride will at first take out most of it even from a fairly strong alkali solution, apparently because it accompanies the other alkaloids that are extracted (it is very hard to separate it completely from thebaine), and the reverse extraction is difficult. But after such a separation has been made, the "porphyroxine-meconidine" can scarcely be

extracted by carbon tetrachloride from alkali, and the reverse extraction, with alkali from carbon tetrachloride, is much easier. In fact, when separated from the other phenolic alkaloids, "porphyroxine-meconidine" has only a slight solubility in carbon tetrachloride, and is difficult to shake out with it even from a slightly ammoniacal solution. Chloroform, however, will still extract it from alkali after it has been separated from the non-phenolic alkaloids. (This is true also of some of the other minor phenolic alkaloids of opium.) From an unbuffered acetic acid solution "porphyroxine-meconidine" is practically not extracted by carbon tetrachloride, but is extracted by chloroform; if the solution is buffered with sodium acetate the alkaloid is then extracted with some difficulty by carbon tetrachloride, or readily by chloroform. The purified alkaloid appears to be more soluble in benzene than in carbon tetrachloride. Its solubility in ether is rather low, and in petroleum ether very slight; but in the presence of the other minor phenolic alkaloids which are soluble in these solvents, it is extracted. Chloroform is a good solvent for "porphyroxine-meconidine", but likely to take out unwanted substances also, not only other alkaloids, but also non-alkaloidal impurities.

The colour reactions of the isolated base are as follows:

HNO_3 — brownish orangish yellow, becoming a stronger orangish yellow.

H_2SO_4 concentrated — strikes red, dissolves brick orange, soon changing to brown.

H_2SO_4 (2 + 1) — negative, slowly pinkish, with heat purple-red.

HCl concentrated — colourless; gradually pink; heated, purple.

Fröhde's reagent (molybdate in sulphuric acid) — strikes red, soon changing to brown, then to very strong deep green to black green.

Mecke's reagent (selenious acid in sulphuric) — strikes brick red, quickly fading and changing to brown, then develops very strong deep green to black green.

Marquis' reagent (formaldehyde in sulphuric acid) — brick red changing to dark brown.

Ferric salt in H_2SO_4 — red changing to brown changing to dark green gradually.

Persulphate in H_2SO_4 — red, at once changing to blue-green, changing to dull green (gradually fading).

The above reactions appear to be clearly related to those of rhoeadine and the alkaloid of *Papaver glaucum*, both of which also give the porphyry or purplish red colour on heating in dilute mineral acid. Their most conspicuous reaction with certain sulphuric acid reagents is: bright red, changing through brown to strong green. Thus the alkaloid of *Papaver glaucum* shows:[26]

H_2SO_4 concentrated — strikes red, at once changing to intense brown-yellow, gradually to intense green.

Marquis' reagent — strikes orange-red, at once changing to intense green.

Rhoedine gives nearly the same. With "porphyroxine-meconidine", the reaction with H_2SO_4 or with Marquis' reagent proceeds only as far as the brown colour, in the time of observation that was used; but with an oxidizing agent present, as with ferric sulphate in H_2SO_4, or persulphate in H_2SO_4, or Fröhde's or Mecke's reagent, the green colour is obtained.

The best way of observing these reactions is to evaporate a little of the solvent containing the alkaloid in a small crucible, and apply the reagent to the thin film of the dry alkaloid on white porcelain.

If the isolated or nearly pure "porphyroxine-meconidine" is heated in (1 + 9) HCl, to transformation to the red compound, and the solution then allowed to stand at room temperature, the red compound very soon precipitates in crystalline form. With a small proportion of other alkaloids present, red-plates may be formed, showing a noticeable dichroism with polarized light (light to deep red). The isolated or nearly purified alkaloid gives dark needles or thin rods, often in rosettes or double sheaves. The test can be made on the microscope slide with a minute amount. When the alkaloid is practically pure nearly all the colour crystallizes out of the acid solution. Since this characteristic property seems not to have been mentioned by preceding investigators, it may reasonably be inferred that they had not even come very close to isolating the alkaloid responsible for the red colour of heated acid solutions.

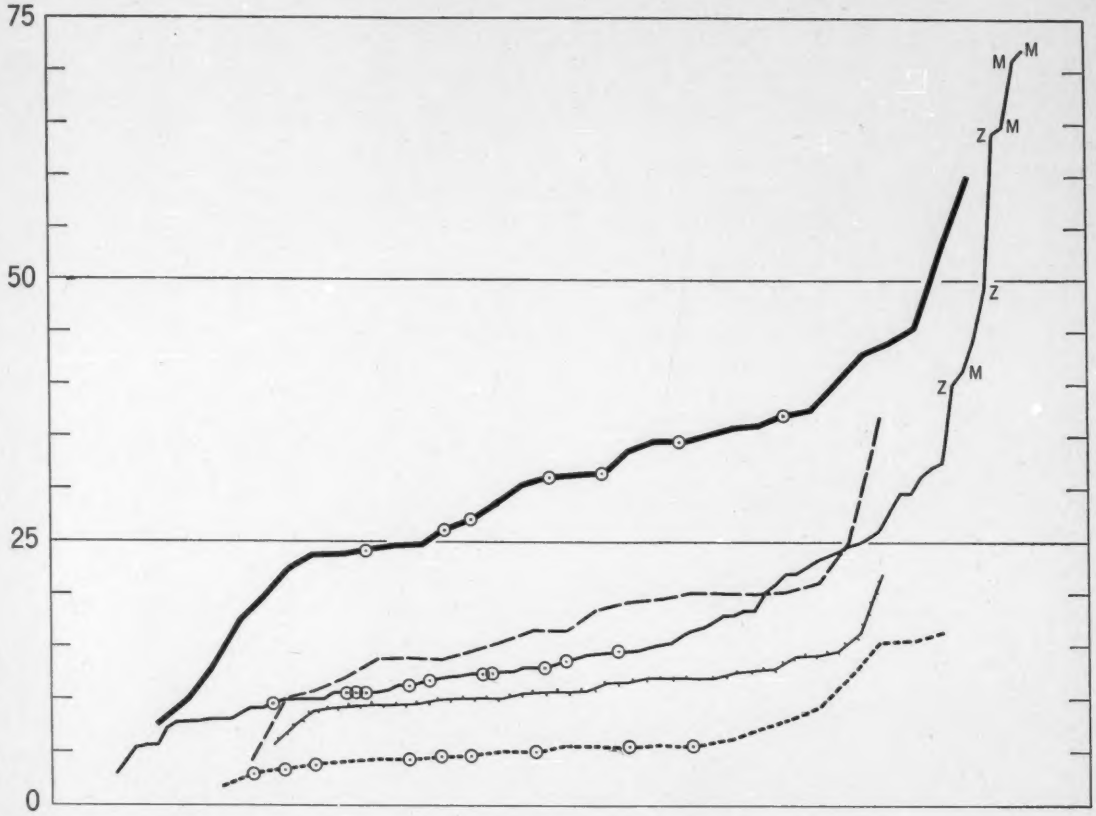
Determination of the Origin of Seized Opium

The possibility of determining the origin of seized opium by chemical and physical tests is currently the subject of an international research programme, in which chemists of Austria, Canada, Denmark, France, Germany, India, Israel, Japan, Netherlands, Norway, Turkey, United Kingdom, and the United States of America, as well as the Secretariat of the United Nations, are taking part.

The Secretariat chemists and the Canadian Government chemists, C. G. Farmilo and P. M. L. Kennett, have studied the utility of a comparative determination of "porphyroxine-meconidine" as a means of determining the origin of seized opium. First results were very promising.[27, 28, 29]

New samples of opium have been contributed to the United Nations chiefly by the producing countries themselves, for international collaborative research. A survey of "porphyroxine-meconidine" in these new samples has been made by the Secretariat, and a paper on the new data has been prepared simultaneously with this article and issued as document ST/SOA/SER. K/4.[30]

The method consists essentially in extracting the opium with lime-water, then extracting a part of the lime-water filtrate (equivalent to one gramme of opium) with ether in a continuous extraction apparatus until no more "porphyroxine-meconidine" is coming over, evaporating off the ether and developing the red or porphyry colour from the alkaloidal residue by heating with 1 per cent HCl. The comparative values are given by the colour developed from the "porphyroxine-meconidine" of one gramme of opium, in 10 cc. solution, read in the one-eighth inch cell in comparison with the red slides of the Lovibond tintometer.



India
Laos and Vietnam
Turkey
Greece and Yugoslavia
Iran

The circles indicate samples of the export opium of India, Turkey, Iran.

Z and M indicate samples from Zile and Malatya (Turkey).

The accompanying chart combines all the available data for five of the main regions of opium production, and shows the comparative results. The curves represent eighty-eight samples from Turkey, thirty-two from India, thirty from Greece and Yugoslavia, twenty-four from Iran and twenty-one from Laos and Vietnam. Horizontally, the samples are simply arranged in their order of value for each curve; they are spaced more

widely apart as the number for the curve is smaller. The ordinates correspond to the colorimetric values obtained for "porphyroxine-meconidine" on the various samples.

Export samples of India, Turkey, and Iran are marked on the curves with circles. The export opium of Turkey is made by mixing all the opium of the country, and thus in itself represents the average of Turkish opium. The export samples of Turkey fall almost entirely on the lower half of the curve for Turkey as represented here. The significance of this is that in obtaining representative samples of different types, the varieties of Turkish opium containing high "porphyroxine-meconidine" have been over-represented, in comparison with the quantity of production. The Turkish export samples (values 9.4 to 14.4) indicate virtually the same curve as found for Balkan opium (Greece and Yugoslavia).

As is clearly seen, the samples from India generally have a much higher value in "porphyroxine-meconidine" than those from other countries. A few samples from Turkey, however, rank with, or even above, the highest of the Indian samples: all but one of these Turkish samples (having values above 35) were from Zile or Malatya, thus showing a regional difference within the larger region of Turkey. In general the samples from Turkey, Laos and Vietnam, Greece, Yugoslavia, and most other countries from which the opium has been examined, gave intermediate values, while those from Iran gave much the lowest values.

Since there is some overlapping of curves, the "porphyroxine-meconidine" value cannot be decisive alone, in determining the origin of seized opium. Rightly used, it is one of the best tests for the chemical determination of origin, particularly in the wide distinction between the usual Indian and Iranian opiums. The different positions of the curves for various countries, and in particular the consistent differences between the export opiums of India, Turkey, and Iran, are eloquent of the relation of "porphyroxine-meconidine" value to origin.

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OFFICIAL

Evolution in 1950 of National Legislations on Narcotics

Pursuant to a resolution of the Economic and Social Council, dated 28 March 1947, the Secretary-General regularly submits to the Commission on Narcotic Drugs a statement on the national laws and regulations relating to the control of narcotic drugs which have been received by the Secretariat during the year.

During 1950[1] the Secretary-General was informed of ten important laws promulgated during the period 1947-1950. Five of them are concerned exclusively with the suppression of the non-medical use of opium. These laws were issued in Burma, the Indian provinces of Assam, Orissa and Punjab, and the United Kingdom Colony of North Borneo. New laws covering the entire narcotics administration were enacted in Iran, in Yugoslavia and in the United Kingdom Colony of Mauritius. Laws dealing primarily with raw materials were passed in Peru and Turkey. Furthermore, much of the new legislation in many countries was concerned with placing synthetic drugs under the existing national controls.

International Co-operation

For the period between June 1950 and June 1951, the following changes took place in the field of international control regarding signatures, ratifications, adherence to or acceptance of international instruments:

Ecuador (8 June 1951), Haiti (31 May 1951), and Iraq (14 September 1950) became Parties to the Protocol of 11 December 1946, amending the agreements, conventions and protocols on narcotic drugs concluded at The Hague on 23 January 1912, at Geneva on 11 February 1925, 19 February 1925 and 13 July 1931, at Bangkok on 27 November 1931 and at Geneva on 26 June 1936.

India (10 November 1950), Indonesia (21 February 1951), the Netherlands (26 September 1950), Turkey (14 July 1950), and the United States of America including all territories for the foreign relations of which it is responsible (11 August 1950), became Parties to the Protocol of 19 November 1948 bringing under international control drugs outside the scope of the Convention of 13 July 1931 for Limiting the Manufacture and Regulating the Distribution of Narcotic Drugs, as amended by the Protocol signed at Lake Success on 11 December 1946.

The Secretary-General received notification that the functions and obligations under the 1912, 1925, and 1931 Conventions, under the Agreements of 1925 and 1931, and under the 1948 Protocol, regarding Laos and Vietnam, were transferred from the Government of France to the Governments of Laos and Vietnam respectively. The Government of France informed the Secretary-General that, as of 1 January 1950, it would no longer furnish separate documents for Algeria, Guiana, Réunion, Guadeloupe and Martinique concerning the implementation of the international conventions, as these territories had become departments of France and therefore integral parts of the French Republic. The Allied High Commission for Germany was reported to have suggested to the Government of the Federal Republic of Germany that, as a condition precedent to assuming responsibility for the control of narcotic drugs, the Government expressly confirm Germany's adherence to the 1912, 1925 and 1931 Conventions and adhere to the 1936 Convention and to the 1946 and 1948 Protocols.

The Government of the Republic of Indonesia stated that, in accordance with the agreements concluded at The Hague in 1949, the international obligations regarding narcotic drugs which had been undertaken by the Netherlands would also be carried out by Indonesia.

The Government of the Netherlands reported that it was preparing to ratify the 1936 Convention.

At the level of regional co-operation, Benelux's Permanent Committee on Public Health established a Narcotics Sub-Committee, which is to harmonize the application of the narcotics laws in Belgium, the Netherlands and Luxembourg.

[1] See document E/NL.1950/Summary.

Scope of Control

While the basic purpose of all narcotic control is the restriction of narcotic drugs to medical and scientific use, certain variations appear in the measures taken by governments to attain that purpose. In Colombia, licences issued for the import, manufacture and sale of drugs are to be reviewed for the primary purpose of protecting public health. In Iran, the Ministry of Hygiene may, with the approval of the Council of Ministers, include in the list of narcotic drugs any product which it seems fit to restrict in the interest of health or morale. In the Indian province of Mysore, licences for import, export, sale, etc., of intoxicating drugs may be issued only for "medicinal, scientific, industrial or like purposes". The Yugoslav control régime was established to "protect the health of the nation and to prevent the unlawful use of narcotic drugs and raw materials"; manufacture and preparation are restricted to medical and scientific purposes and imports to medical and scientific requirements.

Prohibition of Non-Medical Use of Opium

Of the five laws prohibiting the non-medical use of opium communicated to the Secretary-General during 1950, two authorize the issue of smoking licences to existing addicts.

Production of Raw Materials

Regarding the production of raw materials, it is particularly interesting to note the establishment of a Coca Monopoly in Peru, which is to control the sowing, cultivation, harvesting, distribution, consumption and export of coca; the introduction of a zoning system for the production of opium in Turkey and, in a somewhat different form, in Yugoslavia. The Turkish and Yugoslav laws establish government monopolies, not for the cultivation of the raw materials, but rather for the purchase of the crops. The cultivators in designated areas are free to grow or not, provided they comply with certain requirements.

Manufacture

Among the principal provisions dealing with manufacture reported to the Secretary-General, were those adopted in Iran in 1947, providing for the centralization of all manufacture in the capital; and those passed in Yugoslavia in 1950, according to which the manufacture of narcotic drugs is the task of State enterprises under the Federal Government and forms part of the general economic plan. An interesting subsidiary regulation passed in Japan in 1949 institutes a system of special identification marks for all narcotics on the market.

In France, in accordance with the Decree of 19 November 1948, Orders establishing the limits for the manufacture of narcotic substances are issued annually. The Order for 1950, like the one for 1949, authorized the production of morphine, diacetylmorphine, methylmorphine, ethylmorphine, dihydrohydroxycodeinone, dihydrocodeinone, dihydromorphinone, cocaine, their respective salts, and of one synthetic drug, namely: pethidine.

Domestic Trade

Turkey and Yugoslavia reported the introduction of state monopolies for the domestic trade in certain narcotic raw materials. In each case the conversion of these materials, too, is a state monopoly. Peru created a monopoly which controls the distribution, consumption and export of coca. Iran requires pharmacists to submit all requests for narcotic drugs to the Ministry of Hygiene, and medical practitioners need special licences by that Ministry before they may obtain narcotic drugs. The Mauritius Ordinance of 1950, while controlling all transfers by the usual licensing provisions, actually imposes a somewhat similar system, as all drugs imported must be stored at the government store and may be withdrawn only by permission of the Director of Medical Services. Apart from efforts to perfect the licensing systems controlling the movement of narcotic drugs, the following measures were reported: the use of official forms for medical prescriptions of narcotic drugs was reported by Argentina, Brazil, and by the United States of America for the state of California.

In Australia and New Zealand amendments were passed legalizing the keeping of drugs in airplanes for emergency purposes. In the Indian province of Mysore, advertisements of narcotic products were restricted to medical literature. In the United States, the use of *cannabis sativa* for manufacturing fibre was placed under the control of the Commissioner of Narcotic Drugs.

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Measures intended to improve the existing machinery of records, reports and governmental inspection, penal sanctions which various countries enacted for the suppression of the illicit traffic in narcotic drugs, measures relating to the administrative organization of the control of narcotic drugs at the national level, are dealt with in other chapters of the statement of the Secretary-General.

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NOTE TO THE ARTICLE BY WEILL AND WEISS

(Vol. III, No. 2, April 1951)

On page 21 of this article, the preparation of 3-hydroxy-N-methylmorphinane (dromoran) by Grewe, Mondon, and Nolte, Ann. *564*, 161 (1949), and by Schnider and Grussner, *Helv. Chim. Acta, 32*, 841 (1949), is mentioned. It has been called to our attention by Messrs. F. Hoffmann — La Roche & Co., Ltd., that actually the paper by the Swiss authors was submitted earlier, having been received by the editors of *Helv. Chim. Acta* on 11 December 1948. The paper by Grewe *et al.* was received on 15 July 1949.